

## REMARKS

With this amendment, claim 1 has been amended and claims 2-116 have been cancelled without prejudice. Applicants reserve the right to prosecute claims 2-116 in one or more divisional or continuation applications. With this amendment, claims 117-174 have been added. Thus, upon entry of the present amendment, claims 1 and 117-174 will be pending in the present application. Support for the claim amendments to claim 1 and new claims 117-174 is found in the specification in accordance with the following table.

<b>Claim Number</b>	<b>Support for Amendment in the Specification</b>
<p>1. A method for constructing a variant set for <u>modifying</u> a biopolymer of interest, the method comprising:</p> <ul style="list-style-type: none"> <li>a) identifying<del>, using a plurality of rules,</del> a plurality of positions in said biopolymer of interest and, for each respective position in said plurality of positions, one or more substitutions for the respective position, wherein the plurality of positions and the one or more substitutions for each respective position in the plurality of positions collectively define a biopolymer sequence space; <u>and</u></li> <li>b) selecting <u>a first plurality of variants of the biopolymer of interest thereby forming</u> a variant set, wherein said variant set comprises <del>a plurality of variants of said biopolymer of interest and wherein said variant set is</del> <u>comprises</u> a subset of said biopolymer sequence space;</li> <li>c) measuring a property of all or a portion of the variants in the variant set; <u>and</u></li> <li>d) modeling a sequence-activity relationship between (i) one or more substitutions at one or more positions of the biopolymer of interest represented by the variant set and (ii) the property measured for all or the portion of the variants in the variant set <u>and deriving from said sequence-activity relationship (i) a value for the contribution to the measured property by the one or more substitutions at one or more positions of the biopolymer of interest, and (ii) a value quantifying the confidence with which the contribution to the measured property by the one or more substitutions at one or more positions of the biopolymer of interest can be assigned[[:]]</u> <u>and</u></li> <li>e)<del>redefining the variant set to comprise variants that include substitutions in the plurality of positions that are</del></li> </ul>	<p>Original Claim 1; Figure 2; Page 22, lines 10-24; Page 57, line 1, through page 61, line 20</p> <p>Figs. 6 &amp; 7; page 71, line 16, to page 72, line 31; page 73, line 10 to page 74, line 13</p>

Claim Number	Support for Amendment in the Specification
<del>selected based on a function of the sequence-activity relationship.</del>	
2	Original claim 1
3	Original claims 1 and 2
4	Page 21, line 29, to page 22, line 9
<p>120. The method of claim 119, wherein the plurality of rules comprises two or more rules selected from the group consisting of:</p> <p>(i) the favorability of a substitution calculated from a substitution matrix;</p> <p>(ii) the probability of a substitution calculated from a conservation index;</p> <p>(iii) the proximity of a position to a structurally defined region within the biopolymer;</p> <p>(iv) the presence of a substitution in a homologous biopolymer;</p> <p>(v) the favorability of a substitution calculated from a comparison of homologous sequences;</p> <p>(vi) the mutability of a position calculated from a comparison of homologous sequences;</p> <p>(vii) the favorability of a substitution calculated from a comparison of homologous structures; and</p> <p>(viii) the mutability of a position calculated from a comparison of homologous structures.</p>	<p>Page 21, lines 20-21</p> <p>Page 31, lines 1-20</p> <p>Page 31, lines 21-27</p> <p>Page 31, line 33 to page 32, line 20</p> <p>Page 34, lines 24-25; Figure 4</p> <p>Page 34, lines 24-25; Figure 4</p> <p>Page 32, line 21, to page 33, line 27 Figure 4</p> <p>Page 32, line 21, to page 33, line 27 Figure 4</p> <p>Page 32, line 21, to page 33, line 27 Figure 4</p>

<b>Claim Number</b>	<b>Support for Amendment in the Specification</b>
121	Page 58, line 15, to page 61, line 20
122	Page 57, lines 11-13
123	Page 57, lines 11-13
124	Page 57, lines 11-13
125	Section 5.4.3 beginning on page 79, line 28, <i>e.g.</i> , page 80, lines 19-23
126	Page 58, lines 15-34; page 138, lines 12-15
127	Page 58, line 15, to page 61, line 20
128	Page 74, line 1-13
129	Page 58, lines 23-26
130	Section 5.5 beginning on page 87, line 24, <i>e.g.</i> , page 88, line 31 to page 89, line, line 3
131	Page 43, line 24, to page 44, line 14; page 8, lines 19-24
132	Page 8, lines 28-31
133	Original claim 2
134	Original claim 3

<b>Claim Number</b>	<b>Support for Amendment in the Specification</b>
135	Original claim 4
136	Original claim 5
137	Original claim 8
138	Original claim 9
139	Original claim 10
140	Original claim 11, page 66, line 22, through page 67, line 4
141	Original claim 12
142	Original claim 13; Section 5.5 beginning on page 87, line 24, <i>e.g.</i> , page 88, line 31 to page 89, line, line 3
143	Original claim 14
144	Original claim 15
145	Original claim 16
146	Original claim 20
147	Original claim 21
148	Original claim 22
149	Original claim 23
150	Original claim 24
151	Original claim 25

<b>Claim Number</b>	<b>Support for Amendment in the Specification</b>
152	Original claim 26
153	Original claim 27
154	Original claim 28
155	Original claim 30
156	Original claim 36
157	Original claim 37
158	Original claim 38
159	Original claim 41
160	Original claim 42
161	Original claim 43
162	Original claim 45
163	Original claim 51
164	Original claim 52
165	Original claim 53
166	Original claim 54
167	Original claim 60
168	Original claim 61
169	Original claim 66
170	Original claim 44
171	Section 5.2, beginning on page 56, line 25
172	Page 70, line 32, to

Claim Number	Support for Amendment in the Specification
	page 71, line 5
173	As given for claims 1-72 above and page 15, line 20, to page 16, line 27
174	As given for claims 1-72 above and page 15, line 20, to page 16, line 27

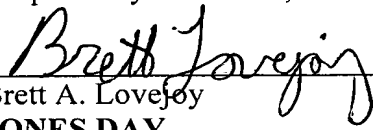
Thus, no new matter has been added by way of the amendments to claim 1 or by the addition of new claims 117-174.

### CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks and new claims 117-174 into the file of the above-identified application. If any fees are due in connection with this submission, please charge the required fee to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

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